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Research Paper

Procalcitonin and Covid-19: Study of a Series From Mohammed Vi University Hospital, Tangier

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ABSTRACT

Aim.

This study aims to investigate association of seral procalcitonin (PCT) level with inflammatory biomarkers, scan extent of lung Injury and mortality in patients with COVID-19.

Methods.

A retrospective monocentric study concerns 113 adult patients with symptoms compatible for COVID-19 in whom SARS-CoV-2 infection was confirmed by RT-PCR test, lung injury was assessed by chest tomography CT and hospitalization required in Covid-19 intermediate or intensive care units in August 2021. All sampling and investigations were performed at patient's admission.

Different clinical characteristics, CT results and admission biological parameters levels, including PCT, were compared across alive and deceased patients. Afterward was searched an association between inflammatory markers and PCT seral level.

Results.

The median age of the 113 patients was 59 years (IQR = 21.5), consisting of 57 men (50.9%). Mostly were not vaccinated (68.1%). In admission, the median extension of lung involvement on CT was 60% (IQR = 25). During follow-up, 52 patients (46%) died.

An inflammatory state in patients was observed, with median CRP 168 mg/l (133 mg/l), median ferritinemia 568 ng/ml (IQR=505) and LDH 581 IU/l (IQR=343). Median procalcitonin was 0.36 ng/ml (IQR=0.91).

The median blood leucocyte count (WBC) was 9080/mm^3 (IQR = 5540). Lymphopenia was common with a median lymphocyte count at 770/mm^3 (IQR = 520). The median neutrophil to lymphocyte ratio (NLR) was 10.12 (IQR = 10.82).

Deceased patients had a more marked inflammatory profile on admission. Indeed, CRP and LDH were significantly lower in surviving patients. Although the majority of patients had lymphopenia, the median blood lymphocyte count was higher in the survivors (820/mm^3 versus 690/mm^3, p= 0.02). Median procalcitonin was significantly higher in deceased patients (0.49 ng/ml versus 0.23 mg/l; p=0.001).

Regarding to PCT levels, the majority of patients had negative PCT (58.4%). Only 6 patients had procalcitonin greater than 10.1 ng/ml. CRP was significantly higher in patients with positive procalcitonin. The same was true for the P/N ratio. Similarly, lymphocytes were lower in patients with positive procalcitonin.

Conclusion.

In patients admitted for COVID-19, procalcitonin is very useful to patients with acute respiratory distress syndrome. Procalcitonin is significantly associated with hospital mortality, suggesting that PCT may represent an excellent prognostic biomarker.

Its seral level is significantly associated with other inflammatory biomarkers as CRP, LDH, PCT, Lymphocyte count and NLR.

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I. INTRODUCTION:

The natural history of SARS-CoV-2 infection includes an initial stage of viral replication, followed by a immuno-pathological stage in which deregulation of the host innate immune response results in a state of hyperinflammation (1) similar to bacterial co-infections (2,3). This inflammatory state may hinder efforts aiming to minimize unnecessary antibiotic prescribing.

In viral respiratory infections, bacterial co-pathogens are important causes of morbidity and mortality. During this pandemic, antibiotic use was high, reaching 75% of cases (4), while meta-analyses have reported a low prevalence of confirmed bacterial co-infection (8%) (5). Thus, antibiotic prescription is significantly higher than the estimated prevalence of bacterial co-infection. To verify the interest of procalcitonin in Covid-19, we conducted this retrospective study evaluating the correlation between procalcitonin and inflammatory biomarkers levels, extent of lung injury on CT scan, and mortality.

II. MATERIAL AND METHODS:

A monocentric retrospective study of 113 patients were met the inclusion criteria: adult age, clinical overview compatible with COVID-19, SARS-CoV-2 infection confirmed by RT-PCR molecular diagnostic test with assessment of the degree of chest involvement by CT and requiring hospitalization in Covid-19 intermediate or intensive care units in August 2021.

The data related to demographics, mortality and laboratory results were collected retrospectively from hospital electronic medical records and from the laboratory information system (LIS).

Serum PCT, CRP, ferritin, LDH, and complete blood count (CBC) sampling were performed at patient admission and measurements were done at the biochemistry laboratory of the University Hospital of Tangier-Morocco, using three automated systems: BC5380 Mindray hematology analyzer for CBC, VIDAS 3 of Biomérieux, ELFA (Enzyme Linked Fluorescent Assay) technique for Procalcitonin, ferritin and the BS 380 biochemistry analyzer of Mindray for the rest of biomarkers.

The initial data collection and processing was carried out with Microsoft Office Excel software and the statistical analysis was performed using the IBM SPSS Statistics software (V.26.0).

III. RESULTS:

Demographic and biological data in the general population

The study involved a total of 113 adults infected with SARS-CoV-2 and admitted to the intensive care units and the resuscitation ward. The median age of the patients was 59 years (IQR = 21.5), consisting of 57 men (50.9%) and 55 women (49.1%).

The majority of the population was not vaccinated (68.1%). Fifteen patients (13.3%) received one dose of live-attenuated vaccine and only 21 patients (18.6%) received a full vaccination schedule. At admission, the median extension of parenchymal lesions was 60% (IQR = 25). During follow-up, 52 patients (46%) died.

Patients had an inflammatory state, with median CRP 168 mg/l (133 mg/l), median ferritinemia 568 ng/ml (IQR=505) and LDH 581 IU/l (IQR=343). Median procalcitonin was 0.36 ng/ml (IQR=0.91).

The median blood leucocyte count (WBC) was 9080/mm3 (IQR = 5540). Lymphopenia was common in this population; the median lymphocyte count was 770/mm3 (IQR = 520). The median neutrophil to lymphocyte ratio (NLR) was 10.12 (IQR = 10.82).

Comparison between alive and deceased patients

Deceased patients had a more marked inflammatory profile on admission. Indeed, CRP and LDH were significantly lower in surviving patients (Table 1). Although the majority of patients had lymphopenia, the median blood lymphocyte count was higher in the survivors (820/mm^3 versus 690/mm^3, p= 0.02).

Median procalcitonin was significantly higher in patients who died (0.49 ng/ml versus 0.23 mg/l; p=0.001).

There were no differences regarding the age or sex of the patients between these 2 groups (Table 2).

Table 1 : Biological data

	Deceased N=52	***Alive N=61***	***p***
CRP (mg/L)	189 (111)	143 (154)	0,001
PCT (µg/L)	0,49 (1,77)	0,23 (0,66)	0,001
LDH (U/L)	632 (395)	555 (337)	0,01
Ferritinemia (ng/mL)	603 (786)	537 (406)	0,68
Lymphocyte count (.10^3 Cell/µl)	0,69 (0,53)	0,82 (0,62)	0,018
Leucocyte count (.10^3 Cell/µl)	10,5 (5,53)	8,14 (4,82)	0,20
Neutrophil count (.10^3 Cell/µl)	9,11 (5,20)	6,43 (4,73)	0,135
N/L Ratio (NLR)	12,76 (12,27)	8,3 (6,64)	0,013

Table 2 : Other datas

	Deceased N=52	*Alive N=61*	*p*
Age (years)	60,5 (18,3)	59,0 (20,0)	0,55
CT extent of lung injury (%)	70 (30)	60 (25)	0,109
Sexe (Male/Female)	30/22	28/33	0,26
Vaccination			0,019
- ***No vaccination***	- 40 (76,9)	- 37 (60,7)	
- ***Incomplet vaccination***	- 8 (15,4)	- 7 (11,5)	
- ***Complete vaccination***	- 4 (7,7)	- 17 (27,9)	

Comparison regarding PCT levels

We divided the population into several groups according to procalcitonin level: less than 0.5 ng/ml, 0.5 to 2 ng/ml, 2.1 to 10 ng/ml, and greater than 10.1 ng/ml (Table 3). Do not exclude patients above 10 given the small population.

The majority of patients had negative PCT (58.4%). Only 6 patients had procalcitonin greater than 10.1 ng/ml.

CRP was significantly higher in patients with positive procalcitonin. The same was true for the P/N ratio. Similarly, lymphocytes were lower in patients with positive procalcitonin.

Table 3 : Association between inflammatory markers and PCT concentrations

	PCT ranges				
	Negative <0,5 N=66	*0,5 to 2 N=26*	*2,1 to 10 N=14*	*Up to 10,1 N=6*	*p*
Age	58,5 (22,5)	59,0 (16,0)	61,0 (14,0)	68,0 (24,0)	0,55
CT extent of lung injury	60 (20)	73 (20)	60 (35)	63 (34)	0,11
CRP (mg/L)	129 (128)	187 (120)	206 (129)	240 (17)	0,001
PCT (µg/L)	0,13 (0,23)	0,78 (0,49)	5,0 (4,21)	22,26 (34,79)	0,001
LDH (U/L)	499 (297)	661 (385)	662 (423)	580 (351)	0,001
Ferritinemia (ng/mL)	546 (590)	524 (411)	816 (768)	555 (681)	0,68
Lymphocyte count (.10^3 Cell/µl)	0,88 (0,62)	0,67 (0,53)	0,58 (0,55)	0,56 (0,52)	0,018
WBC count (.10^3 Cell/µl)	8,3 (6,13))	10,04 (5,98)	10,6 (3,6)	7,2 (8,15)	0,20
Neutrophil count (.10^3 Cell/µl)	6,9 (5,5)	8,5 (5,9)	9,1 (4,2)	6,1 (7,2)	0,135
NLR	8,5 (7,9)	10,11 (11,2)	16,1 (24,1)	12,1 (14,5)	0,013

IV. DISCUSSION:

Physiologically, thyroid C cells and pulmonary neuroendocrine cells synthesize, at first, pre-procalcitonin, which will become procalcitonin (pro-hormone) after cleavage of a signal sequence by endopeptidases. Procalcitonin is the precursor of calcitonin obtained by enzymatic conversion. Serum procalcitonin levels are very low (<0.01 ng/mL) in physiological conditions. However, in infection case (bacterial, parasitic or deep fungal), microbial antigens trigger the elevation of PCT synthesis. Secretion starts about 4 hours after the onset of sepsis and can reach a peak of up to 10.000 times the basal concentration within 6 to 12 hours with an elimination half-life of 25 to 30 hours. This is under the influence of a pro-inflammatory cytokine cascade releasing endotoxins and/or cytokines that act on various tissues (IL-6, TNF-α and IL-1b...). In contrast, after viral infection, the released cytokines (INF-γ...) result in down-regulation of PCT, thus highlighting another benefit of PCT measurement.

Because COVID-19 disease is potentially fatal and highly contagious, risk stratification can help triage patients, guide treatment and monitor disease progression and treatment. In non-COVID-19 settings, elevated PCT is associated with bacterial rather than viral infections (6), whereas in COVID-19 studies, elevated PCT concentrations are observed and are associated with poor prognosis (7,8) and defining thresholds to diagnose bacterial co-infections is proving difficult (9). Procalcitonin (PCT) may provide additional diagnostic discrimination (10). Especially in view of the lack of specificity of radiological manifestations, the lack of sensitivity of microbiological examinations as well as the limitation of CRP and white blood cell count, which only partially exclude co-infections (2,11).

The risk to get very sick from COVID-19 increases for older adults. As the median age of our patients was 59 years. An Italian study (n= 1074), suggests that procalcitonin may represent an excellent prognostic biomarker for COVID-19, especially in geriatric patients (>75 years) (12).

Studies show that the death rate is still far higher among unvaccinated people than among the vaccinated ones (13). In our study, patients vaccinated against COVID-19 are significantly less to die (p=0,019).

Studies have shown that high PCT level is associated with worse clinical outcomes (7,8)**.** In our patients, the mean procalcitonin was significantly higher in deceased patients 0,49 ng/ml (1,77) than in survivors 0,23 ng/ml (0,66) (p=0,001). While a meta-analysis of 10 cohort studies (n=7716) showed that higher procalcitonin is positively associated with the severity of COVID-19, which is a potential biomarker for assessing the severity of COVID-19 and predicting prognosis (14). In another study of Afro-Caribbean patients

in New York (n=271), procalcitonin was the only factor strongly associated with both mortality and ICU acceptance (15).

Our results are explained by the fact that the biological assessments studied are performed at admission of patients who were hospitalized only around J8 - J10 of their Covid-19 infection and that those with high PCT were superinfected and were managed and cured of their bacterial superinfections and also survived. However, for the group of patients who died, their lower mean PCT indicates that they required hospitalization rather in relation to the extent of inflammation and not superinfection.

In our series, the means of biomarkers are significantly higher in non-survivors than in survivors and significantly so for CRP 189 (111) versus 143 (154) (p=0.001), for LDH 632 (395) versus 555 (337) (p=0,01) and NLR 12,76 (12,27) versus 8,3 (6,64) (p=0.013). Depending on the procalcitonin range, there is a significant association with inflammatory biomarkers as CRP (p=0,001), LDH (p=0,001), PCT (p=0,001), Lymphocyte count (0,018) and NLR (0,013).

CRP has limited discriminatory value (2) and PCT has been increasingly used to provide greater diagnostic certainty. According to an English study (published in 2016), CRP can be used in the early diagnosis of pneumonia (16), and patients with severe pneumonia had high CRP levels. In the Covid-19 context, studies have shown that the cost of measuring PCT is significantly higher than CRP or WBC count on CBC (17), and elevations of PCT, CRP, and WBC count can be concordant (7). Indeed, procalcitonin determination has not been done in all patients hospitalized with Covid-19.

Several studies have used low PCT values, allowing exclusion of bacterial co-infections, to safely reduce antibiotic prescription (7,17,18).

Regarding the association of chest CT score with inflammatory mediators, the chest CT score of patients with COVID-19 is associated with the severity of the systemic inflammatory response (19). Correlation analysis of a Chinese study (n=108) indicated that the chest CT score had significantly positive correlations with white blood cell count ($P = 0.001$), neutrophil count ($P < 0.001$); CRP ($P < 0.001$), procalcitonin ($P < 0.001$), serum ferritin ($P < 0.007$) and a negative correlation with Lymphocyte count ($P < 0.001$) (19). In our patients, CT scan extension in deceased patient is more than non-survived 70 (30) versus 60 (25) (p=0,109). the correlation between the CT extent of lung injury and the level of PCT was not significant (p=0.11).

The limitations of our study are its retrospective and monocentric nature, the modest sample size, and the absence of information on antibiotic therapy prior to hospitalization.

V. CONCLUSION:

In Covid-19 context, procalcitonin is very useful to patients with acute respiratory distress syndrome. Procalcitonin is significantly higher in deceased patients. Its seral level is significantly associated with other inflammatory biomarkers as CRP, LDH, PCT, Lymphocyte count and NLR.

Larger prospective studies and randomized controlled trials will define the relationship between PCT level and bacterial co-infections in COVID-19 to guide antibiotic prescribing, in order to reduce the selection of resistant species and to limit drug toxicities.

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